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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/626,275	07/24/2003	Ernest J. Lee	PC28017	9606

23913 7590 07/23/2010

PFIZER INC
Mary J Hosley
150 EAST 42ND STREET
MS: 150/02/E112
NEW YORK, NY 10017-5612

EXAMINER	
SCHLIENTZ, NATHAN W	
ART UNIT	PAPER NUMBER
1616	

NOTIFICATION DATE	DELIVERY MODE
07/23/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

~IPGSNY@Pfizer.com

Office Action Summary	Application No.	Applicant(s)	
	10/626,275	LEE ET AL.	
	Examiner	Art Unit	
	Nathan W. Schlientz	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 May 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-10,12-15,20 and 24-41* is/are pending in the application.

4a) Of the above claim(s) *26 and 27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-10,12-15,20,24,25 and 28-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/24/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 1, 3-10, 12-15, 20 and 24-41 are pending in the present application. Claims 26-27 remain withdrawn from further consideration as being directed to non-elected subject matter. Thus, claims 1, 3-10, 12-15, 20, 24, 25 and 28-41 are examined herein on the merits for patentability. No claim is allowed at this time.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 24 February 2010 was filed after the mailing date of the non-final Office action on 12 November 2009. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered by the examiner.

Withdrawn Rejections

Rejections and/or objections not reiterated from the previous Office Action are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of rejections and/or objections presently being applied to the instant application.

Declaration under 37 CFR § 1.132

The declaration filed 12 May 2010 has been considered and is discussed herein below along with responses to applicant's arguments.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 1, 3-10, 12-15, 20, 24, 25 and 28-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The instant claims recite “no more than about”, “greater than about”, “at least about” and “not greater than about”. A range, such as no more than, greater than, at least, and not greater than, implies that the recited value is above or below a distinct value. The term “about” implies that values other than the recited value are encompassed within the range. Therefore, it is unclear where the range begins and ends and what values are encompassed by the range. It is recommended that applicants delete the term “about” from the ranges in order to clarify the distinct end point values of each range.

Response to Arguments

Applicant argues on pages 8-10 that the term “about” is not indefinite and one of ordinary skill in the art, in light of the instant specification, would readily be able to determine whether they are infringing on the instant claims. However, the examiner respectfully argues that the terms ”no more than about”, “greater than about”, “at least

about", and "not greater than about" are indefinite because "no more than", "greater than", "at least", and "not greater than" indicate values that are within a specific range, but the term "about" implies that the end point is variable. Therefore, it is not clear what values fall within the instantly claimed ranges.

2. Claim 15 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 15 recites, "a fluctuation ratio that is not substantially greater than that of an equal daily dose of an immediate-release pramipexole dihydrochloride reference formulation, administered three times daily". However, "not substantially greater than" is indefinite because it is not clear what is intended by "substantially greater". The term "substantially greater" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Response to Arguments

Applicant argues on page 11 that the instant specification at Table 8 provides sufficient insight into what the term "not substantially greater" means. However, Table 8 compares Mirapex with three examples of the instant invention, but does not define the term "not substantially greater than". Therefore, one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1,148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

1. Claims 1, 3-10, 12-15, 20, 24, 25 and 28-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Holman (US 6,277,875) in view of Pospisilik '240 (US 2002/0103240) and Vandecruys et al. (WO 00/59477) (cited in the IDS filed 29 April 2004).

Determination of the scope and content of the prior art

(MPEP 2141.01)

Holman teaches a composition comprising pramipexole dihydrochloride monohydrate as the active ingredient and as inactive ingredients lactose hydrous, pregelatinized starch, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, purified water, carnauba wax, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, synthetic iron oxide, and polysorbate 80 (col. 11, ln. 35-46).

Homan teaches treating patients with pramipexole at a dose of 0.125 mg once per day at bedtime (qhs) followed by gradually increasing the active on a weekly basis until the patient exhibits a therapeutic effect or intolerance (col. 9, ln. 59 to col. 10, ln. 4). Holman teaches administering pramipexole at up to 6.0 mg qhs (Table 1), wherein the effective dose of pramipexole is usually between about 0.125 mg qhs to about 15.0 mg qhs, more usually between about 0.25 mg qhs and about 6.0 mg qhs (col. 10, ln. 5-36).

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

Holman does not explicitly disclose the *in vitro* release profile and the *in vivo* absorption profile as instantly claimed. However, Pospisilik '240 teaches controlled release pellet or tablet compositions may be produced using pramipexole, such as a mixture of a pramipexole salt, a suitable filler, and a suitable release controlling agent ([0064]). Vandecruys et al. teach controlled release compositions comprising an active ingredient (i.e., anti-Parkinsonian drugs), pregelatinized starch and a hydrophilic polymer, wherein the combination of pregelatinized starch and hydrophilic polymer affords controlled release that is safeguarded or maintained in release media of changing ionic strength, i.e. along the entire gastrointestinal tract both in fasted as well as in fed conditions (Abstract; pg. 4, ln. 32 to pg. 5, ln. 3; and pg. 8, ln. 9). Vandecruys et al. further teach an example wherein the controlled release composition resulted in 11.99% release of the active ingredient at 1 hr, 17.74% release at 2 hr, 25.8% release at 4 hr and 33.26% release at 6 hr (Table 5).

Finding of *prima facie* obviousness

Rational and Motivation (MPEP 2142-43)

Therefore, it would have been *prima facie* obvious for one of ordinary skill in the art to formulate pramipexole as a controlled release formulation wherein the drug is administered once daily and exhibits the *in vitro* release profile and the *in vivo* absorption profile as instantly claimed.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to Arguments

Applicant, as well as Dr. Heimlich, argues that in view of Pospisilik one of ordinary skill in the art would not be able, with a reasonable expectation of success, to arrive at a sustained release formulation according to the instant invention. However, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Pospisilik clearly provides sufficient motivation with a reasonable expectation of success for preparing controlled release pramipexole formulations. Pospisilik states that it can be done, and even states that in order to prepare controlled release formulations you would add a suitable filler, e.g. microcrystalline cellulose, and a suitable release controlling agent comprising water and/or a water-insoluble

macromolecular substance. Therefore, one of ordinary skill in the art would want to look into the relevant art (i.e., controlled release pharmaceuticals) in order to determine a suitable formulation for controlled release pramipexole. It is also well-known to prepare sustained release formulations that exhibit similar efficacy to multiple dosage immediate release formulations of the same drug, since the immediate release formulations are administered multiple times in order to maintain a therapeutically effective amount within the plasma. Starches in combination with hydrophilic controlled release polymers have been readily used in the art in order to formulate controlled release pharmaceutical agents, as evidenced by Vandecruys et al. Vandecruys et al. teach controlled release compositions comprising an active ingredient (i.e., anti-Parkinsonian drugs), pregelatinized starch and a hydrophilic polymer, wherein the combination of pregelatinized starch and hydrophilic polymer affords controlled release that is safeguarded or maintained in release media of changing ionic strength, i.e. along the entire gastrointestinal tract both in fasted as well as in fed conditions. Therefore, it would have been well within the purview of one of ordinary skill in the art to formulate controlled release pramipexole formulations wherein administration once a day results in the same bioavailability as immediate release formulations. It also would have been well within the purview of one of ordinary skill in the art to determine the necessary amounts of filler, such as microcrystalline cellulose, and control releasing agent in order to achieve the desired controlled release profile.

2. Claims 1, 3-10, 12-15, 20, 24, 25 and 28-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pospisilik '240 (US 2002/0103240) in view of Vandecruys et al. (WO 00/59477).

Determination of the scope and content of the prior art

(MPEP 2141.01)

Pospisilik '240 teaches controlled release pellet or tablet compositions may be produced using pramipexole comprising a mixture of pramipexole salt, a suitable filler, such as microcrystalline cellulose, and a suitable release controlling agent comprising water and/or a water-insoluble macromolecular substance such as an acrylate polymer or a modified cellulose ([0064]). Pospisilik '240 further teaches that pramipexole is commercially available as the dihydrochloride salt ([0004]).

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

Pospisilik '240 does not teach the controlled release of pramipexole to comprise a starch and a hydrophilic polymer and have an *in vitro* release profile wherein at 2 hours no more than 20% pramipexole has dissolved, or an *in vivo* absorption profile wherein the time to reach a mean of 20% absorption is greater than about 2 hours and/or the time to reach a mean of 40% absorption is greater than about 4 hours, as instantly claimed. Pospisilik '240 also does not teach the controlled release pramipexole wherein the pramipexole is in the form of a dosage unit that is given as a daily dose in one dosage unit, as instantly claimed.

However, Vandecruys et al. teach controlled release compositions comprising an active ingredient (i.e., anti-Parkinsonian drugs), pregelatinized starch and a hydrophilic polymer, wherein the combination of pregelatinized starch and hydrophilic polymer affords controlled release that is safeguarded or maintained in release media of changing ionic strength, i.e. along the entire gastrointestinal tract both in fasted as well as in fed conditions (Abstract; pg. 4, ln. 32 to pg. 5, ln. 3; and pg. 8, ln. 9). Vandecruys et al. further teach an example wherein the controlled release composition resulted in 11.99% release of the active ingredient at 1 hr, 17.74% release at 2 hr, 25.8% release at 4 hr and 33.26% release at 6 hr (Table 5).

Finding of *prima facie* obviousness

Rational and Motivation (MPEP 2142-43)

Therefore, it would have been *prima facie* obvious for one skilled in the art at the time of the invention to prepare controlled release pramipexole dihydrochloride salt compositions, as taught by Pospisilik '240, wherein the controlled release compositions comprise pregelatinized starch and a hydrophilic polymer and are suitable for once daily administration, as reasonably taught by Vandecruys et al.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to Arguments

Applicant's arguments are the same as above. Therefore, the examiner's response above is incorporated herein by reference.

3. Claims 1, 3-18, 20 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pospisilik '119 (US 2004/0068119) in view of Vandecruys et al. (WO 00/59477).

Determination of the scope and content of the prior art

(MPEP 2141.01)

Pospisilik '119 teaches controlled release pellet or tablet compositions may be produced using pramipexole comprising a mixture of pramipexole salt, a suitable filler, such as microcrystalline cellulose, and a suitable release controlling agent comprising water and/or a water-insoluble macromolecular substance such as an acrylate polymer or a modified cellulose ([0061]). Pospisilik '119 further teaches that pramipexole is commercially available as the dihydrochloride salt ([0004]).

Ascertainment of the difference between the prior art and the claims

(MPEP 2141.02)

Pospisilik '119 does not teach the controlled release pramipexole to have an *in vitro* release profile wherein at 2 hours no more than 20% pramipexole has dissolved, or an *in vivo* absorption profile wherein the time to reach a mean of 20% absorption is greater than about 2 hours and/or the time to reach a mean of 40% absorption is greater than about 4 hours, as instantly claimed. Pospisilik '119 also does not teach the controlled release pramipexole wherein the pramipexole is in the form of a dosage unit

that is given as a daily dose in one dosage unit administered at one time, as instantly claimed.

However, Vandecruys et al. teach controlled release compositions comprising an active ingredient (i.e., anti-Parkinsonian drugs), pregelatinized starch and a hydrophilic polymer, wherein the combination of pregelatinized starch and hydrophilic polymer affords controlled release that is safeguarded or maintained in release media of changing ionic strength, i.e. along the entire gastrointestinal tract both in fasted as well as in fed conditions (Abstract; pg. 4, ln. 32 to pg. 5, ln. 3; and pg. 8, ln. 9). Vandecruys et al. further teach an example wherein the controlled release composition resulted in 11.99% release of the active ingredient at 1 hr, 17.74% release at 2 hr, 25.8% release at 4 hr and 33.26% release at 6 hr (Table 5).

Finding of *prima facie* obviousness

Rational and Motivation (MPEP 2142-43)

Therefore, it would have been *prima facie* obvious for one skilled in the art at the time of the invention to prepare controlled release pramipexole dihydrochloride salt compositions, as taught by Pospisilik '119, wherein the controlled release compositions comprise pregelatinized starch and a hydrophilic polymer and are suitable for once daily administration, as reasonably taught by Vandecruys et al.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole would have been prima facie obvious to

one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Response to Arguments

Applicant's arguments are the same as above. Therefore, the examiner's response above is incorporated herein by reference.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nathan W. Schlientz whose telephone number is (571)272-9924. The examiner can normally be reached on 9:00 AM to 5:30 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann R. Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

NWS

/John Pak/
Primary Examiner, Art Unit 1616